Technology to provide transtelephonic interpretation of digital images is available (312).

Finally, study of the economics of incorporation of echocardiography into routine evaluation of chest pain in the ED, or of basing triage decisions on its results, has yet to be done. In early 1997, the NHAAP Working Group on "Evaluation of Technologies for Identifying Acute Cardiac Ischemia in the ED" (207,233) concluded that even in highly selected groups, the sensitivity of echocardiography was not sufficient to warrant its use for triage and risk stratification in the ED. There remains a lack of comparative, prospective clinical trial information on the diagnostic performance, clinical outcomes and costs of using early echocardiography for risk stratification and triage decisions in chest pain evaluation in the ED (313–315).

**Stress echocardiography.** Stress echocardiographic testing may be useful for risk stratification of patients with negative cardiac markers or normal rest echocardiographic data before discharge. The incremental value of stress echocardiographic imaging over standard ECG stress testing remains to be determined. This is particularly true in patients with baseline normal ECGs and in other groups (e.g., women, young men) in whom false positive rates for ECG stress testing are relatively high (316,317).

**Conclusions.** Given the technical limitations, resource requirements and somewhat limited sensitivity and incremental value of echocardiography in the ED setting, this modality should have further prospective study in comparison with standard strategies before recommending its widespread use in acute chest pain evaluation.

**Myocardial perfusion imaging in patients presenting to the ED with an ACS.** Investigations from the late 1970s documented the power of planar thallium-201 imaging to predict outcomes in patients presenting with ACSs (318–320). New technetium-99m–based radiopharmaceutical agents for myocardial perfusion are better suited for early use by allowing "uncoupling" of the injection from imaging and providing concurrent evaluation of function (321–325). For optimal value, it is preferred that early perfusion imaging be provided daily on a 24 h basis. The principal barriers to providing this service around the clock are cost and timeliness of radiotracer availability. In patients with an ACS, the optimal value of imaging requires injection during or as soon as possible after symptoms start (326). This can only be accomplished if radiotracer is available in the ED and an in-house staff member is available to perform the injection at all times.

Clearly, the availability of imaging capability in or next to the ED is optimal. All imaging studies should be performed as gated tomographic acquisitions (327). Image interpretation should be performed by physicians with expertise in nuclear cardiology, using both static perfusion and gated functional images, as well as a cine film of the rotating acquisition to evaluate patient motion and artifact. In the case of a negative early imaging study, an appropriate follow-up evaluation is indicated.

**Repeat presenters to the ED with negative findings or indications for coronary angiography.** Among the low risk patients with chest pain who present to the ED, there is a subgroup with a pattern of repeat visits with consistently negative cardiac findings and unrevealing evaluations for noncardiac etiologies of their symptoms (328). These patients account for a disproportionate number of ED visits for chest pain among the entire group with negative findings. In these patients, it is reasonable to consider cardiac catheterization and coronary angiography to document the absence of cardiac disease or to identify an unsuspected cardiac condition. A normal evaluation may significantly relieve the cardiac focus and anxiety of many patients and thereby decrease the number of ED visits when symptoms arise. Negative findings also provide essential information to the physician for management decisions in subsequent ED visits by these patients with chest pain. In addition, the detection of unsuspected cardiac disease by catheterization affords the potential for definitive management.

## SUMMARY

Safe, cost-effective management of patients presenting to the ED with chest pain is a continuing challenge. The traditional low threshold for admission of these patients, in order not to miss a life-threatening cardiac condition, has resulted in a <30% incidence of coronary events in those admitted for chest pain. This approach has been neither medically optimal nor cost-effective. It is now recognized that the high and low risk groups of patients presenting with chest pain can be recognized on presentation, facilitating urgent therapy for the former and more deliberate evaluation of the latter. Chest pain programs have been developed for systematic implementation of innovative approaches. Most CPCs focus on the low risk group and utilize accelerated diagnostic protocols, usually comprising 6 to 12 h of monitoring and serial cardiac biomarkers, which, if negative, are followed by stress testing (exercise ECG or noninvasive cardiac stress imaging). These methods have been safe and accurate and appear to be cost-effective. Most patients in the low risk group with negative evaluations have a noncardiac source of the chest pain, but follow-up evaluation for noncardiac etiologies has been inadequate and could improve care of these patients.

## RECOMMENDATIONS

1. Nontraumatic chest pain in adults presenting to the ED should prompt evaluation for an ACS.
2. Evaluation of chest pain should follow a comprehensive, systematic, protocol-driven approach with the goals of identifying 1) myocardial necrosis; 2) ischemia at rest; and 3) stress-induced ischemia.

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3. The goals of initial assessment of the patient with chest pain are 1) to distinguish patients with an ACS or other serious etiology; 2) to assess the level of risk of adverse outcomes in patients with a suspected ACS or other serious etiology; and 3) to initiate rapid treatment in patients with serious conditions, according to current published guidelines.
4. Patient evaluation in the ED should include documentation of diagnostic tests and management in coordination with the patient's primary care physician and, when appropriate, with a cardiologist.
5. Patients with negative evaluations for ACS should have further studies for noncardiac causes of chest pain.
6. Chest pain centers facilitate rapid, efficient management of high risk patients with an ACS and identification of lower risk patients who do not require hospital admission, by application of accelerated diagnostic protocols.
7. Chest pain centers may have a dedicated environment and the coordinated efforts of specialized personnel or may utilize personnel and process ("virtual units") to attain the objectives of safe, accurate and cost-effective management of patients presenting with chest pain.
8. Accelerated diagnostic protocols should include 6 to 12 h of observation, ECG monitoring, serial cardiac biomarkers and, in patients with negative findings, stress testing before discharge.
9. Expertise in the recognition of typical and atypical presentations of ischemic chest discomfort is mandatory for physicians managing patients with this presentation.
10. An ECG should be obtained and interpreted within 10 min or less of presentation of the patient with chest discomfort, and, when possible, it should be recorded in the presence and absence of chest discomfort.
11. Right-sided ECG leads should be recorded in patients with evidence of inferior or posterior MI.
12. Posterior ECG leads ($V_7$ through $V_9$) should be recorded in patients in whom posterior infarction is suspected.
13. The role of continuous ST segment monitoring in the ED has not been established.
14. The results of cardiac biomarker testing should be available within 30 to 60 min in patients presenting with a possible ACS.
15. Because of their superior sensitivity and specificity for identifying myocardial injury, the cardiac troponins are currently the biochemical markers of choice for this purpose.
16. Guidelines and critical care pathways are useful in that they emphasize a systematic program for the management of patients presenting with chest discomfort and provide a basis for quality assurance, but they do not replace clinical judgment. These guidelines also emphasize the need for a functional design of the program, appropriate staffing, quality assurance and outreach.
17. Standard echocardiography cannot be recommended for routine use in the ED evaluation of patients presenting with chest discomfort because of technical limitations, resource requirements and limited incremental diagnostic value.
18. Early rest nuclear imaging for risk stratification of patients presenting with a possible ACS can be effectively employed in institutions with appropriate resources and expertise and can be cost-effective if patient volume is sufficient.
19. The majority of patients presenting with acute chest discomfort who have negative cardiac findings have a noncardiac etiology of their symptom, which may be gastrointestinal, musculoskeletal, pulmonary or psychological. These patients require further evaluation to provide a basis for appropriate management.
20. Coronary angiography should be considered in selected patients with repeat presentations to the ED for chest discomfort with negative cardiac evaluations and no other identifiable source of symptoms.

# Task Force 3: Special Aspects of Research Conduct in the Emergency Setting: Waiver of Informed Consent

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In the U.S., nearly 1,000 people die each day after experiencing a sudden, out-of-hospital cardiac arrest. Although standard-of-care resuscitation efforts are applied on behalf of most of these patients, the mortality rate is nevertheless as high as 99% in some urban areas. The American College of Cardiology (ACC) strongly advocates a vigorous program of

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medical research directed at improving these very dismal outcomes. Because these patients are deprived of their autonomy by their sudden cardiac arrest, the ACC also believes it is essential to maintain these patients' rights as human beings during the course of their enrollment and treatment as research subjects. Although informed consent is one of the usual means of providing for such protection, it is usually impossible in such emergency situations where no "informing" or "consenting" can occur because of sudden death or critical illness. Because therapy is highly time dependent, and even 2 or 3 min can dramatically reduce survival, consent by family members or other surrogates is equally difficult.

Because critically ill and dying patients who are unable to give consent are often individuals for whom new advances are likely to be life-saving, the Food and Drug Administration (FDA) and National Institutes of Health (NIH) have recognized that conditions for the conduct of research in these patients must be specified (329). The recently promulgated FDA regulations stipulate the conditions for ethical research when the informed consent requirement is waived. Examples of abuse of patients' rights from the recent past, most notably from the Department of Energy's radioactive materials studies, have underscored that such oversight of the conduct of research is imperative (330).

Unfortunately, confusion and uncertainty about the application of these regulations are significantly impairing the national research community's efforts to improve the outcomes of these most severely ill Americans. Implementation at the local level of the new regulations for cardiac arrest victims and other emergency patients (329) is currently vague and burdensome. The nation's research projects, and thus its efforts to improve the outcomes of cardiac arrest, were stopped entirely between 1993 and 1996. During this period, no waiver of informed consent was valid. Furthermore, since the end of the moratorium and the adoption of these new regulations, new projects are proceeding very slowly, at a rate of less than two studies per year. The task of this working group was to address and attempt to establish clearer rules. We will begin by examining some of the history that has led to efforts to protect human subjects.

## PRE-1993 INFORMED CONSENT REGULATIONS

Much of the debate and confusion over informed consent begins with the first principle of the Nuremberg Code, which states that "the voluntary consent of the human subject is absolutely essential" (see the event timeline in Table 1 for important dates surrounding informed consent) (331). This document did not address the need for research on subjects who could not, for any number of reasons, give their own "voluntary consent" (332), but focused on unethical research conducted in Nazi Germany, which deprived healthy individuals of their autonomy. Research on subjects who cannot give informed consent requires other means to ensure that the research is ethical and the patients' rights are protected. It is widely recognized that informed consent is not always needed for research to be considered ethically acceptable. The World Health Organization's Declaration of Helsinki recognized that incompetent patients could be subjects of research if consent was obtained from a proxy, and went further to say that consent could be waived altogether "if the physician considers it essential not to obtain informed consent, the specific reasons for the proposal should be stated in the experimental protocol for transmission to the independent committee" (332).

The research community in the U.S. recognized the need for a waiver of consent to allow research on patients who could not give consent. Two major government regulatory agencies that dealt with research (Department of Health and Human Services [DHHS] and FDA) developed different but unfortunately inconsistent regulations on the criteria for waiver of informed consent. Under the regulations

**Table 1.** Timeline of Events Surrounding Informed Consent

| | |
|---|---|
| 1932 | U.S. Public Health Service begins the Tuskegee Syphilis Study (333). |
| 1946–1947 | Nuremberg Tribunal: "the voluntary consent of the human subject is absolutely essential." |
| 1964 | Declaration of Helsinki (334): recognized that a proxy decision-maker is ethical for subjects who lack decision-making capacity. |
| 1972 | Tuskegee Syphilis Study terminates (333). |
| 1979 | National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: The Belmont Report (335): articulated three principles for research—respect for persons, beneficence and justice. |
| 1992 | Public outcry over testing without consent, as performed by the Department of Energy on subjects with ionizing radiation (330). |
| 1993 | "Dear Colleague" letter from OPRR at NIH warns Institutional Review Board chairs that deferred consent does not meet regulatory compliance for waiver of consent (336). |
| 1994 | The FDA terminates an ongoing human CPR study and sends marshals to the homes of investigators to confiscate devices. |
| | Rep. Ron Wyden, Chairman of the House Subcommittee on Regulation, Business Opportunities and Technology, holds a public hearing on waiver of consent in the emergency setting. |
| 1995 | FDA and NIH co-sponsor public meetings to discuss issues of informed consent. |
| | Initial draft of proposed new rules released in September (337). |
| 1996 | Final new rules released in October for waiver of consent criteria (337). |
| 1997 | President Clinton formally apologizes to the Tuskegee study subjects. |

CPR = cardiopulmonary resuscitation; OPRR = Office of Protection from Research Risks.

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**Table 2.** Pre-1993 DHHS Policy on Waiver of Informed Consent

| The Department of Health and Human Services (i.e., NIH) allowed a waiver of consent only if all of the following were true: |
|---|
| 1. The research involves no more than minimal risk to the subjects. |
| 2. The waiver will not adversely affect the rights and welfare of the subjects. |
| 3. The research could not practically be carried out without the waiver. |
| 4. Subjects are provided with additional pertinent information after participation, as appropriate. |

developed by DHHS, researchers could get a waiver of consent if four criteria were met (Table 2). However, a major problem developed because of the requirement that the research involve no more than minimal risk. This "no more than minimal risk" clause seemed to preclude almost all emergency research, because these situations were likely to involve more than minimal risk. However, some emergency research was carried out under this regulation when investigators interpreted minimal risk to mean the differential risk in outcome for the experimental treatment as compared with standard treatment, not the risk compared with the risks of daily life. In addition, "deferred consent" was used in some studies. Under deferred consent, a patient was initially entered into the study, and then later, when the patient became competent or a proxy was identified, consent (or no consent) to remain in the study after initiation of therapy was obtained. Different organizations interpreted these practices and regulations differently.

During this period, the FDA regulations allowed for a waiver of informed consent for nonresearch "compassionate use" purposes, only using different criteria (Table 3). A serious difficulty with these criteria was the use of the phase "necessary" to save the life of a patient, as this seemed to eliminate the use of control groups. It was impossible to claim that participation in the placebo arm of a trial was "necessary" to save a life. These ambiguities created multiple problems for researchers, Institutional Review Boards (IRBs) and regulatory agencies. Concerns were being expressed that studies were done "outside of the rules." Some IRBs would approve a study, whereas other IRBs would reject the same study. Some investigators and companies would not even consider initiating the efforts and resources to advance a proposal owing to the confusing situation. To make matters even worse, many studies required both NIH and FDA oversight and had to meet both sets of criteria.

**Table 3.** Pre-1993 Food and Drug Administration Regulation on Waiver of Informed Consent

| The FDA permitted a waiver of consent for nonresearch "compassionate use" if all four of the following conditions were met: |
|---|
| 1. The human subject is confronted with a life-threatening condition necessitating the use of a device or drug. |
| 2. Informed consent cannot be obtained from the subject because of an inability to communicate with or obtain legally effective consent from the subject. |
| 3. Time is not sufficient to obtain consent from the subject's legal representative. |
| 4. There is no alternative method of approved or generally recognized therapy available that provides an equal or greater likelihood of saving the life of the subject. |

## THE 1993 "MORATORIUM" ON EMERGENCY RESEARCH

The issue came to a crisis in 1993, when the Director of the Office of Protection from Research Risks (OPRR) at the NIH warned IRB chairs in a "Dear Colleague" letter that using deferred consent was not in compliance with DHHS rules on waiver of consent and that any type of consent mechanism that did not involve prospective waiver of consent was not in compliance (336). The effect of this letter was to place a moratorium on all human resuscitation research in the U.S. The fear of regulatory action against the research community became real when the FDA sent armed U.S. marshals to the homes of CPR investigators to confiscate suction-cup devices when the FDA terminated a study in progress because of concerns about informed consent. An IRB had approved this trial, and no apparent adverse effects had been noted at the time of the suspension. The FDA also terminated a study on head trauma owing to informed consent issues and only allowed enrollment of patients for whom informed consent could be obtained prospectively in an antioxidant study.

Multiple efforts began to develop new rules for waived consent that would permit emergency care research on impaired subjects. A national consortium of emergency care researchers was created. Rep. Wyden, Chairman of the House Subcommittee on Regulation, Business Opportunities and Technology, held a public hearing on waiver of informed consent in the emergency setting. A new set of rules was distributed in September 1995, additional hearings took place and a final rule was adopted in October 1996 (337). The 1996 final FDA rule allowed waiver of informed consent under a limited set of criteria (Table 4, abridged version).

## AFTER THE 1996 FINAL RULE (21 CFR 50.24)

With the final rules for waiver of informed consent published in 1996, the way for a waiver of informed consent on new studies seemed to be clear. The FDA hosted a "National Conference on Implementation of the Waiver of Informed Consent in Emergency Situations" on September 29–30, 1997. The new rule and issues of implementation were described, and public commentary was solicited (338). There was substantial controversy over the new rules. Since then, most written statements in the published data have

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**Table 4.** Abridged Highlights of the 1996 Food and Drug Administration Rule (21 CFR 50.24)

The central themes of the final 1996 rule were:
1. The patient has a life-threatening situation.
2. Available therapies are unproven or unsatisfactory.
3. Direct consent from the patient is not feasible because of the patient's condition and because therapies must be started before an authorized surrogate representative can be contacted.
4. The research cannot be reasonably conducted otherwise.
5. The risks and benefits of the experimental protocol are considered reasonable in light of the patient's condition and what is known about the other available therapies.
6. Participation in the research holds out the prospect of direct benefit to the subject.

been supportive of the final rules; some strong opposition was also voiced (337,339). Some critics suggested that the new rules were regressive and in violation of the Nuremberg Code. They also questioned the claim that the patient may benefit from experimental therapy (339).

Although these rules allow for waiver of informed consent under very limited circumstances, they also created a new set of obstacles for researchers: they require a vaguely defined community consultation and a public disclosure program (336,339–341). Santora et al. (340) described the stepwise process followed at the Allegheny University of the Health Sciences to comply with the requirement for public disclosure. This procedure required 80 person-hours to complete and included four public meetings, newspaper notices, radio public service announcements and a 24 h telephone hotline. Another report of efforts to comply with the new rules revealed that the institution had to increase community representation on their IRB, fund newspaper notices, create a call-in telephone line, hold public forums, make presentations to the Department of Medicine and Medical Boards, create a videotape presentation, provide literature in the physician lounge, put up large posters, put brochures in patient rooms and have charge nurses notify patients (342). A total of 25 people from a community of nearly 1.5 million people attended the public forum. The direct costs for the public disclosure was $5,600. A total of four patients were enrolled in the study over four months. The authors reported confusion as to what was sufficient for a broad community consultation/public disclosure criterion.

If the "public disclosure" dilemmas were not enough for researchers, a survey of what patients actually think about the 1996 FDA rule (21 CFR 50.24) suggests an even rockier road ahead for the rules. Smithline and Gerstle (343) surveyed a convenient sample of 212 emergency patients. Only half of the patients were in agreement with a waiver of consent for serious illness, using the new rules. This discordance between patient desires and regulatory requirements will likely lead to future conflicts for the research community.

In addition, the following new procedural protections are required: 1) consultation with the community in which the research will occur; 2) informing the subject, if feasible, representative or family member at the earliest point, including in the event of death; 3) public disclosure of the study results when completed; 4) use of an independent data safety board; and 5) approval of the study by the FDA.

## STATEMENT OF THE PROBLEM

Traditional informed consent for human research is impossible or difficult in a number of common medical conditions. The Emergency Department or the prehospital care environment is often the site where such emergencies occur, even if one limits the focus to cardiovascular conditions. Informed consent is usually impossible to obtain during cardiac arrest, acute congestive heart failure, sepsis or hemorrhage, stroke syndrome, drug overdose with hemodynamic compromise, severe hypoxia related to acute or chronic pulmonary disease, severe metabolic acidosis and alteration in sodium or hydration with altered mental status. There are also a number of conditions for which "consent" can be obtained from the patient, even though it is likely that the detailed and prolonged explanation may not be fully understood by the patient. Such circumstances might include circulatory catastrophes requiring an immediate intervention (e.g., ruptured ventricle, valve or aorta), massive hemorrhage, pulmonary embolism with severe hypoxemia, congestive failure with shock, myocardial infarction with severe pain or dyspnea, life-threatening arrhythmia with hypotension or hypertensive crisis. A "standard of reasonableness" with regard to the adequacy of informed consent is often not met.

Research requiring informed consent or a waiver in such settings would include not only new therapeutic strategies but also studies involving a protocol approach to medical effectiveness, or implementation of care plans with a research focus that involves more than minimal risk. Minimal risk is usually limited to drawing a very small amount of venous blood, blood testing and data gathering.

## ISSUES IN OBTAINING INFORMED CONSENT IN EMERGENCY SITUATIONS

The FDA requires that the investigators attempt to obtain informed consent from the patient "under all reasonable conditions" (337). A waiver of informed consent is only considered where informed consent is not possible.

Intense efforts to obtain informed consent before circumstances such as a cardiac arrest raise a number of issues worthy of consideration. These issues include whether informed consent from an individual who is not yet a candidate for a study and is not yet experiencing an emergency is a valid consent. A patient who is not yet a candidate may be more concerned about avoiding candidacy than receiving treatment should a catastrophe occur. Would an individual refuse consent in the belief that consent would

lead to less effort by the provider to avoid candidacy? Alternatively, would a subject agree to participate in a study if he or she believes their candidacy is unlikely, to please a physician or investigator and to gain more attention?

A second issue raised by an intense effort to obtain informed consent before an emergency situation is the number of informed consents needed to gain one patient candidate. What is the psychological impact on a patient of the approach for consent in the event of an adverse outcome that has only a 1 in 500 chance of occurring? If large numbers of patients are to be consented, how detailed does the consent need to be?

Finally, the ability of a patient to understand detailed information during an emergency may be severely compromised. Is there a role for an abbreviated consent procedure with a simple level of understanding, rather than a detailed form, which would be appropriate in the nonemergency setting? We believe it is not reasonable to attempt to obtain informed consent before medical circumstances that may come under study for many patients with cardiac disease.

## JUSTIFIABLE RESEARCH AND CLINICAL EQUIPOISE

Imperatives during biomedical research include an improved understanding of illness and, through this knowledge, better diagnosis, treatment and prevention. However elegant and conclusive preclinical research on a new device, drug or concept may be, diagnostic and therapeutic strategies must be tested in patients before widespread use.

Publication of a clinical trial testing streptomycin as a treatment for tuberculosis nearly 50 years ago led to widespread use of clinical trial methodology in testing new drugs and surgical techniques (344,345). The demand for properly conducted, randomized, controlled animal experiments and clinical trials before general use has protected patients from useless or toxic therapy, although the ethical correctness of clinical trials has been debated periodically (346,347). The requirement for clinical equipoise and informed consent protects patients from exposure to poorly designed and dangerous clinical trials.

As noted earlier, clinical equipoise is the state in which the medical community, after careful review of the totality of evidence, is convinced that none of the therapies tested in a randomized trial are clearly established to be more effective (348). Trial design may compare a therapy with placebo or the best-established therapy (i.e., standard of care). Periodic review of the data developed during the course of a trial by a duly constituted Data and Safety Monitoring Board (DSMB) assures that clinical equipoise remains for the entire research period. If, at any time, one therapy is clearly shown to be superior to another, the DSMB has the duty to terminate the study.

A critical part of the Nuremberg Code (349) and the Declaration of Helsinki (350) is the requirement to inform all subjects involved in medical experimentation before entry into a study. They must know the goals of the experiment and the potential risks, benefits and alternatives. They have the right to withdraw from the study at any time. This is particularly true of vulnerable populations, such as children, those who are mentally impaired or prisoners.

Respect for a subject's autonomy is the underlying ethical principle of informed consent. An important aspect of informed consent is the capacity to understand the goals of the research effort and the attendant risks, benefits and alternatives. Patients brought to medical attention in the midst of a severe illness, particularly an illness that disables the central nervous system, may not be able to give informed consent and can be thought of as having a disability. This is particularly true for patients who have a cardiac arrest. Relatives or friends who might be able to communicate the patient's wishes are often not available in a time frame that would permit entry into a trial using time-sensitive treatments.

Such "disabled" men and women are unable to participate as subjects in a randomized, controlled study using traditional safeguards. The aggregate effect of intellectually disabled patients not getting into clinical trials has resulted in little or no progress in testing new, potentially effective treatments for such severe illnesses. These patients are desperately ill; some never recover; and many die. Holding informed consent in abeyance requires strict documentation of initial and continuing equipoise and may need the involvement of community leaders, including those without ties to medicine or research.

## ETHICAL PERSPECTIVE ON WAIVING INFORMED CONSENT

Clinical research places individuals at risk to develop generalizable knowledge that can be used to improve societal health and well-being. By placing some at risk for the good of others, clinical research has the potential to exploit its subjects. To justify the risks of clinical research and ensure that subjects are not exploited, seven ethical requirements must be met (Table 5).

First, subjects should be placed at risk only when the research concerns a socially, scientifically or clinically important question—one that can improve overall health and well-being. In this sense, "me too" studies are not valuable and not ethically justifiable. Next, the research plan must be valid scientifically; it must offer a good chance of answering the question(s) posed. In this sense, only good clinical research can be justified ethically. Studies that are underpowered or not generalizable or that use biased statistical techniques are not ethical. Third, subjects must be selected in a fair manner. Fair subject selection requires that risky research not be limited to the underprivileged, nor that potentially beneficial research be extended to the privileged. Rather, inclusion and exclusion criteria and subject recruitment strategies must be based on scientific criteria relevant to the information sought. Fourth, research should offer the most favorable risk-benefit ratio possible. To meet this

**Table 5.** Seven Requirements That Make a Research Trial Ethical

| Requirement | Explanation | Justifying Ethical Values |
|---|---|---|
| Social or scientific value | Evaluating a treatment, intervention or theory that will improve health and well-being or increase knowledge. | Scarce resources and avoidance of exploitation |
| Scientific validity | Stating a clear hypothesis, using accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data. | Scarce resources and avoidance of exploitation |
| Fair subject selection | Selecting subjects so that stigmatized and vulnerable individuals are not selected for risky research, while favored classes are offered potentially beneficial research. | Distributive justice |
| Favorable risk-benefit ratio | Minimization of potential risks and harms with maximization of potential benefits so that the risks to the subject are proportionate to the benefits to the subject and society. | Nonmaleficent, beneficence, nonexploitation |
| Independent review | Review of the design of the research trial, its proposed subject population and risk-benefit ratio by an individual who is unaffiliated with the research. | Minimizing potential conflicts of interest, public accountability |
| Informed consent | Provision of information to potential subjects about the purpose of the research, its potential risks, benefits and alternatives, so that the individual understands this information and can make a voluntary, uncoerced decision about participation in the study. | Respect for subject autonomy |
| Respect for potential and enrolled subjects | Respect for subjects by 1) permitting withdrawal from the research; 2) protecting privacy through confidentiality; 3) informing of newly discovered risks or benefits; and 4) informing about the results of clinical research. | Respect for subject autonomy and welfare |

requirement, the risks of research must be minimized and the potential social and individual benefits maximized. When the potential benefits to individual subjects are proportionate or outweigh the potential risks they face, clinical research is ethical. When the potential benefits to individual subjects do not outweigh the risks to them, as in phase I research, then clinical research is justified only when its potential social benefits outweigh the "excess" risks to individual subjects. Although the first comparison of benefits and risks to the same individual is fairly clear and performed routinely, the comparison of social benefits to individual risks is more complex and lacks a clear methodology. Fifth, because investigators may have conflicts of interest between safeguarding subjects and completing their research, and because research must be accountable publicly, research studies should be reviewed by an independent body with the expertise to evaluate the study and the power to approve, revise or even stop it. Sixth, when possible, research subjects should provide informed consent before research enrollment, and continuing consent periodically throughout their participation. Finally, ethical clinical research requires that investigators respect potential and enrolled subjects. This includes respecting subjects' privacy, informing them of what is learned from the research and carefully monitoring their welfare, even if it means withdrawing them from the research if the harms and side effects become too great.

Valid informed consent requires the completion of four separate steps. The first three steps constitute the *informed* portion of the requirement. Subjects must be informed concerning the research study that they are being asked to participate in, including its objective, procedures, risks, potential benefits and alternatives. Second, they must understand this information. Third, physicians and researchers must inform subjects about their medical condition, including their diagnosis and prognosis; subjects must also understand this information. Finally, in the *consent* portion, subjects must make a voluntary decision whether to enroll on the basis of this information, and in light of their own preferences and values.

Why is informed consent important ethically and what are the special ethical concerns raised by conducting human subject research without it? Obtaining informed consent before research enrollment helps to respect subjects' autonomy by allowing them to decide whether or not to enroll. In addition, because individuals are typically in the best position to judge their own interests and values, requiring informed consent increases the chances that individuals will be enrolled in research only when it is consistent with their personal preferences and values. Therefore, conducting

**Table 6.** How Well Do Food and Drug Administration Provisions Satisfy Requirements for Ethical Research and Address Ethical Concerns of Waiving Consent?

| Provision | Ethical Requirement or Concern Addressed |
|---|---|
| 1. IRB approval | Independent review |
| 2. Life-threatening situation without satisfactory treatment | Value |
| 3. Informed consent not feasible | Informed consent when possible |
| 4. Prospect of direct benefit | Most favorable risk-benefit ratio<br>Potential for unwanted research enrollment |
| 5. Risks are reasonable | Most favorable risk-benefit ratio<br>Potential for unwanted research enrollment |
| 6. Impracticable to conduct research without waiver | Informed consent when possible |
| 7. Commitment to contact legally authorized representative | Respect for enrolled subjects |
| 8. Community consultation | Independent review<br>Potential for especially risky research with waiver |
| 9. Public disclosure of research plan | Independent review<br>Potential for especially risky research with waiver |
| 10. Public disclosure of research results | Respect for enrolled subjects |
| 11. Independent oversight board | Independent review<br>Respect for enrolled subjects |
| 12. Investigator informs subject, representative or family member at earliest possible point | Respect for enrolled subjects<br>Ethical concern that waiver of informed consent will diminish respect for subject autonomy |
| 13. Investigator provides information about subjects who die before notification | Respect for enrolled subjects |

IRB = Institutional Review Board.

research without informed consent raises two ethical concerns: 1) investigators may fail to respect subjects' autonomy; and 2) individuals may be enrolled in research that conflicts with their preferences and values.

The emergency setting frequently does not offer sufficient time to inform potential subjects of the nature of the research or obtain their consent. In addition, the ailments on which emergency research focuses—such as stroke, myocardial infarction and acute brain injury—frequently render individuals incapable of understanding during the time treatment must be initiated. For these reasons, research in the emergency setting often cannot meet the four conditions for informed consent. As a result, the ethical conduct of emergency research often depends on the possibility of waiving the requirement for informed consent.

Arguments in support of waiving informed consent in limited cases focus on three claims. First, because many emergency treatments are unproven or unsatisfactory, it is important to identify more effective alternatives. Second, in a related way, because many emergency interventions have dismal outcomes, subjects may benefit—or not be harmed, as compared with conventional care—from enrolling in emergency research.

Finally, by using other safeguards, it is possible to ensure that the interests of individuals who are enrolled in emergency research without their consent are protected and that they will not be exposed to excessively risky procedures.

The FDA regulations allow for a waiver of informed consent before enrollment in emergency research under the 13 conditions outlined in Table 6. The study and waiver are approved by the relevant IRB.

To what extent do these 13 conditions ensure that emergency research conducted without informed consent meets the seven requirements on ethical research? In addition, do these conditions satisfactorily address the special ethical concerns raised by waiving informed consent?

The FDA regulations address the requirement for social, scientific or clinical value by stipulating that subjects must have a life-threatening condition; available treatments must be unproven or unsatisfactory; and the collection of valid scientific evidence must be necessary to determine the safety and effectiveness of particular interventions (condition 2). Presumably, when these conditions are met, the development of alternative treatments has social value. However, two problems arise. First, there is some vagueness in this condition: how unsatisfactory must the treatments be to justify research without informed consent? Is a 10% success rate of the conventional intervention or a 25% success rate sufficiently bad? Is a 50% survival rate with 30% permanent brain injury sufficiently bad? The difficulty here is that the regulations do not require a minimal level of value to justify research without informed consent, nor would it be reasonable to provide such arbitrary limits.

The FDA regulations address the requirement that clinical protocols present the most favorable risk-benefit ratio possible by stipulating that participation must hold out the prospect of direct benefit to the subjects (condition 4) and risks must be reasonable (condition 5). These conditions ensure that subjects of emergency research do not face excessive risks or participate in research with no potential for benefit. However, these conditions do not fully address the special ethical concern that a waiver of informed consent

may lead to individuals being enrolled in research that conflicts with their preferences. Even if most individuals are willing to participate in research that offers the most favorable risk-benefit ratio, these conditions do not ensure that emergency research in which consent is waived meets this condition—a reasonable level of risk can outweigh an unspecified potential for direct benefit.

To address this concern, the American Medical Association guidelines (351), as well as the preamble to the FDA regulations, argue that informed consent should not be waived unless there is clinical equipoise (337). When it does, individuals enrolled in emergency research without their consent will not face a less favorable risk-benefit ratio than individuals who receive standard of care; hence, there is good reason to believe that such enrollment will not conflict with the individual's preferences. However, the FDA's stated conditions—that subjects must have a life-threatening condition, available treatments must be unproven or unsatisfactory and collection of valid scientific evidence must be necessary to determine the safety and effectiveness of particular interventions—are not equivalent to clinical equipoise. These conditions do not compare the experimental treatment being studied directly with any existing standard treatments, which are necessary to assess equipoise. As a result, they do not ensure that clinical equipoise exists.

Although it is very difficult to fully address the possibility of unwanted research enrollment, the regulations would need to address the possibility that some individuals may have idiosyncratic preferences and values that get left out of the assessment of equipoise. For example, the risks from a treatment arm that involved a blood transfusion might be deemed low by most individuals in our society, but would be considered extremely risky to many Jehovah Witnesses.

The FDA conditions provide for significant independent review in addition to the usual IRB review (condition 1). Investigators who request a waiver must establish an independent monitoring board (condition 11) and consult with community representatives (condition 8). In addition, they must disclose their research plan and results (conditions 9 and 10) publicly. Such a comprehensive level of independent review ensures that research without informed consent is not likely to expose subjects to excessive risks. Indeed, combining the conditions for a favorable risk-benefit ratio with this added level of independent review obviates an important concern that informed consent is meant to address—namely, that research could be so risky as to pose a threat to individuals and conflict with subjects' preferences.

The FDA regulations require that investigators obtain informed consent when possible, by stipulating that requests for a waiver may be approved only when the research could not be carried out practicably without the waiver (condition 6) and obtaining consent is not feasible (condition 3). In addition, they ensure that proxy consent is not possible, by requiring that investigators attempt to contact a legally authorized representative for each subject (condition 7).

The regulations define consent as not being "feasible" in terms of three conditions: 1) subjects are not able to give consent owing to their medical condition; 2) the intervention being tested must be administered before it is feasible to get proxy consent; and 3) it is not possible to identify subjects prospectively. Taken together, these conditions go a long way toward ensuring that research without informed consent is done only when necessary.

The FDA regulations address the need to respect potential and enrolled subjects by requiring investigators to attempt to contact a legally authorized representative or family member and that subjects be notified at the earliest time possible (condition 12). This last requirement also helps to address the special ethical concern that research without informed consent fails to respect individuals' autonomy. Finally, for subjects who die before notification, the regulations stipulate that information be provided to the legally authorized representative or family member when feasible (condition 13).

Overall, the FDA regulations go a long way toward ensuring that the ethical requirements for clinical research are fulfilled in emergency research where subject consent is not possible. In particular, attention to the risk-benefit ratio and comprehensive independent review beyond IRB review ensures that subjects unable to consent will not be enrolled in excessively risky research. Although there remain some areas of disagreement, mostly about how difficult it should be to obtain consent before the waiver can be invoked, the conditions do ensure that emergency research with the waiver will fulfill the other ethical requirements.

## PROBLEMS RELATED TO THE FDA/DHHS REGULATIONS ALLOWING A WAIVER OF INFORMED CONSENT

Although the FDA/DHHS regulations have been assessed to be ethical in terms of their requirements for special patient protections, there still exist a number of ambiguities that make the application difficult, hence making them susceptible to misinterpretation and misapplication. A few specific examples of problems related to the interpretation of the regulations follow.

There must be disclosure to the community in which the clinical investigation is to be conducted. The question is, what constitutes adequate community notification? A wide variety of approaches to this difficult problem have been used, including newspaper advertisements, interviews with media, open discussions, meetings with concerned citizen groups, and many of these approaches involve considerable cost and considerable time and delay. What is adequate?

The FDA provisions also require community consultation. What constitutes reasonable consultation? What if there is limited objection to the study as a whole? It is important to point out that the FDA provisions do not

require public input into the study protocol. Instead, it requires community consultation, but what occurs during community consultation cannot by itself block the conduct of the study. Community consultation might raise issues that the IRB has not considered. It is up to the IRB, in conjunction with the investigator, to determine whether these community concerns are sufficient to warrant a change in the protocol. There is absolutely no requirement in the FDA regulations indicating that a community can have direct input into changing the study. Instead, a community's responsibility is to raise concerns that should then be considered by the IRB and the investigator.

Finally, these regulations governing waiver of informed consent have particularly imposing aspects for IRBs and institutional leaders. The regulations require provision of the information to the patient as soon as possible. When alert, the patient must be informed that he or she was included in a research study and provided the option for discontinuation of involvement. If the person does not resume consciousness or succumbs to the illness, the next of kin or immediate family member must be informed immediately of the patient's inclusion in a research study without informed consent. In the latter situation, there is great concern of litigation. It is interesting to note that the same provisions were developed when deferred consent was applied.

The risk of litigation would likely be reduced if there was very detailed documentation of appropriate adherence to the guidelines and regulations. Because the regulations for community notification and public input are currently extremely broad, it will be difficult to legally defend the measures taken as adequate.

## PROPOSAL FOR A NATIONAL CONSENSUS ADVISORY BODY

The 31st Bethesda Conference on Emergency Cardiac Care proposes a national advisory consensus body (committee). There is precedent for the creation of a governmental advisory body related to an area of research in which there is significant public concern. The Recombinant Advisory Committee (RAC) was established in 1974 in response to public concerns regarding the safety of manipulation of genetic material through the use of recombinant deoxyribonucleic acid (DNA) techniques. This body was established as an advisory to the Director of the NIH and focused on concerns "that recombinant DNA technology would be associated with possible hazards relating to new types of organisms, some potentially pathogenic, that could be introduced into the environment without effective controls." The RAC developed a set of guidelines for the use of recombinant DNA materials that have been revised repeatedly since 1976. The guidelines include a comprehensive description of facilities and practices intended to prevent unintended release or exposure to genetically modified organisms. Compliance with these guidelines was made mandatory at institutions receiving NIH funds for research involving recombinant DNA. Many companies complied with the NIH guidelines voluntarily and had representatives that were part of the RAC draft meetings and deliberations. The Director of the NIH was required to seek the advice of the RAC before taking specific actions, including changing containment levels for types of experiments that are specified in the NIH guideline; assigning containment levels for types of experiments that are not explicitly considered in the NIH guidelines; certifying new "vector" systems; promulgating and amending a list of classes of recombinant DNA molecules to be exempt from NIH guidelines; adopting other changes in NIH guidelines; and interpreting and determining containment levels on the request of other regulatory bodies.

The RAC was described as a technical committee whose goals were to consider the current state of knowledge and technology regarding DNA recombinants, their survival in nature and the potential for transfer of genetic materials to the organism. It also considered hypothetical hazards and methods of monitoring and minimizing risk. Approximately one-third of the 25 members did not have scientific expertise, but represented public interest and attitudes. This balance was intended to provide a forum for open public debate of social and scientific issues associated with recombinant DNA research. The RAC is viewed as being overwhelmingly successful in achieving this goal. Recently, review of all protocols by the RAC was discontinued after 24 years, but the group maintains its advisory role. These statements are paraphrased from the Missions Statement of the Recombinant DNA Advisory Committee (352).

The issues surrounding a waiver of informed consent for the conduct of research with more than minimal risk bear similarity to the public concerns with regard to the use of recombinant DNA materials in human and other research efforts. First and foremost, such a national voluntary advisory body dealing with research to be conducted with a waiver of informed consent could provide quality control on the research itself. The advisory body would be composed of a significant number of scientific and physician experts in the areas of emergency cardiac care and would be available to assess the issue of importance of research to be conducted with a waiver of informed consent. Does the state of medical knowledge now allow an acceptance of equipoise between the proposed arms of the study? Is there a valid possibility that treatment of this disease will be improved through inclusion in the intervention arm of the study? Are the risks considered to be reasonable by broad and nationally respected groups of physicians and scientists? Will the study design that is proposed have a high probability of success in demonstrating which of the alternative strategies is more effective? Are the end points that are proposed measurable and important? Is the sample size reasonable for assessing the primary and secondary end points of the proposed study? Making such judgments could be either advisory to the local IRBs, the FDA, the NIH, or sponsors.